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Review

Outline of a concept for organismic systems biology

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ABSTRACT

For several decades experimental biology and medicine have both been accompanied by a dichotomy between reductionistic and anti-reductionistic approaches. In the present paper it is proposed that this dichotomy can be overcome if it is accepted that research on different organizational levels of the organism is necessary. The relevance of such an approach becomes much clearer using an appropriate concept of the organism. The proposed concept is called "organismic systems biology" and is a compilation of three related theories, which are basically in line with considerations of many other organismic thinkers. However, it is argued, that this integrated concept is able to clarify basic assumptions of organicism. The theories are: the systems approach of Paul Weiss, the developmental systems theory and the theory of increasing autonomy in evolution. The hypothesis is that the different levels of organismic functions, which are described by these theories, are necessarily interrelated, thus generating the autonomy of the organism. This principle of interrelation needs to be regarded in scientific reasoning and can be crucial for solving many medical problems.

1. Introduction

There is a long standing debate in the diverse fields of life sciences about the relevance and significance of reductionistic versus holistic concepts of research. These views form different approaches to understanding organisms and influence research programs, interpretations of experimental results and medical interventions in a very profound way. This discussion has been more intensive in biology [1–7], however, in medicine it has been of fundamental importance as well [8–15]. For further readings see [16].

I agree with Brigandt and Love [16] that the thereby generated reductionism versus anti-reductionism terminology has tended to create a false dichotomy between two extreme positions: on the one hand reductionism as the idea that molecular biology can in principle *fully explain* all biological facts – making higher level biological theories dispensable – and on the other hand anti-reductionism as the idea that higher level biological fields possess explanatory principles of their own in the sense of *not benefiting* from molecular biology. Between these two extremes a variety of intermediate positions exists that has motivated many of the efforts seen in alternative as well as in conventional research programs. I will propose that the task of science on different levels of organization becomes much clearer if we use an appropriate concept of the organism.

In recent years critical discussions by some scientists have again arisen upon the assumption that today's biology is due for a conceptual revolution, that it needs to develop a new framework to describe life in a way that better matches the actual properties of the organism and of life itself [3–5,10,17–22]. However, the described dichotomy and the difficulties of some of the older standpoints are seen as a search for something like a new synthesis, not a revival of the old debates. What is being questioned are not the results and the significance of molecular research in itself, but rather the one-sidedness in focusing exclusively on chemical and physical processes with the expectation that living systems can be fully explained from this perspective. This also includes the widespread analogy that sees the organism as a machine and its functions as "mechanisms". Major setbacks and unfulfilled expectations increasingly suggest that these critiques are justified and point to a central problem of modern life sciences.

Woese [3] requests "a new biology for a new century" and assumes that the extreme reductionism developed in many disciplines of biology during the 20th century might have been a necessary and unavoidable transitional stage in the overall course of biology. However, "a biology viewed through the eyes of fundamentalist reductionism is an incomplete biology. Knowing the parts of isolated entities is not enough. A musical metaphor expresses it best: molecular biology could read notes in the score, but it couldn't hear the music. . . . The time has come to replace the purely

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reductionist 'eyes-down' molecular perspective with a new and genuinely holistic, 'eyes-up' view of the living world, one whose primary focus is on evolution, emergence, and biology's innate complexity." (p. 175).

Similar views are shared by many molecular biologists today and this has fueled the widespread interest for systems biology. However, I will argue that the common approach to systems biology appears to be fundamentally flawed and does not really overcome reductionism.

Woese [3] continues: "Let's stop looking at the organism purely as a molecular machine. The machine metaphor certainly provides insights, but these come at the price of overlooking much of what biology is. Machines are not made of parts that continually turn over, renew. The organism is. Machines are stable and accurate because they are designed and built to be so. The stability of an organism lies in resilience, the homeostatic capacity to reestablish itself. While a machine is a mere collection of parts, some sort of 'sense of the whole' inheres in the organism, a quality that becomes particularly apparent in phenomena such as regeneration in amphibians and certain invertebrates and in the homeorhesis exhibited by developing embryos." (p. 176).

Polanyi [23] deals with these questions in an absolutely visionary paper already in the late 1960s.

Richard Strohman, as many authors before him, focuses especially on genetic reductionism which maintains that all processes of an organism can finally be reduced to the level of the gene and that the gene is the ultimate control agent. He leaves no doubt about how important the discoveries of genetics are. However, he does state that the original concept to study genes has illegitimately been extended to explain the whole organism [24]. This is especially demonstrated by the results of recent genetics, which show many anomalies that do not match with what has been expected from a gene centered view. Strohman wrote " . . . Cell and molecular biology, in conjunction with new theoretical developments, have, in the past decade, taken us from a grossly naïve view of genetic determinism (that complex traits are caused by a single gene) to the stark reality that almost all human diseases are complex context-dependent entities to which our genes make a necessary, but only partial, contribution."(p. 701).

Next, I propose an outline of an organismic theory which avoids the one-sidedness of reductionism versus holism. Organicism is the point of view that living organisms are complex, hierarchically structured systems, whose parts are all functionally integrated into and coordinated by the system. This view is shared by many scientists who are looking for a more appropriate approach to the phenomena of life. Organicism brings thinking about organisms closer to the actual phenomena of life. To achieve this I do not invent some new model or theoretical construction, but use insights organismic thinkers have often formulated before, but which have hardly been regarded seriously in mainstream biology. Basically these ideas were developed from empirical experience rather than theoretical considerations. It is a sort of synthesis of the work of some researchers, who were not convinced by the assertion, that organisms, including humans, are nothing more than a product of their molecules, a mostly unexpressed und unconscious claim that dominates large fields of science today, but has never has been proven.

The concept will be compatible with the empirical knowledge which has been gained by today's research programs. However, some interpretations will look different due to this concept. Thus there is no conflict with them but rather the knowledge will be adjusted to its appropriate place.

Essentially the concept refers to three theories, which have a common denominator although they are formulated from different perspectives. Subsequently I will discuss the relevance of the synthesized theory for biology and medicine as well as its difficulties. Then I shall argue that a renewed and much more appropriate research program is accessible for "a biology of the new century".

2. Analysis and synthesis

The first one of these theories comes from Paul Alfred Weiss (1898–1989). He was an Austrian scientist who moved to the United States, where he became a leading figure in science of his time [25]. His contributions to neurophysiology and developmental biology are well known. However, curiously enough his systems approach is nearly forgotten. Only occasionally is his concept cited, but there has hardly been any understanding of this fundamentally unique approach, which differs essentially from most of the usual approaches of systems biology today. Only recently there have been publications which appreciate the concept in a more profound way and argue for a revival of his ideas [26–28]. In the present volume Drack and Wolkenhauer also include the common ground with the work of Bertalanffy [28].

I propose that Weiss comes quite close to what the basic features of an organism really are (see [27] for more information about the history of his ideas). However, it is most impressive that recent research results step by step support his view. Or formulated the other way round: many results become better understandable in the light of his approach.

Weiss develops a perspective, which is suited to understand the organism as well as organs and cells as integrative units, a notion still poorly understood and largely neglected in biomedical science [29–36]. Weiss characterizes the relation of analysis and synthesis and describes how we first recognize nature as an immense cohesive continuum. Then we start to identify discrete fragments in it and isolate single entities to learn more about their exact properties. Subsequently we find out that modifications of such an entity, that may be called entity A, are regularly associated with a series of modifications in another entity called B. By studying this regularity a rule can be established from which all future correlations between A and B can be extrapolated. We then proceed to study A in its relation to C, and C in its relation to B, and so on, to learn how different parts of nature, erstwhile mentally dissected and separated, are actually interdependent. At this stage it is expected that it should be possible to turn the process around – either physically or mentally in our imagination – linking by way of consecutive synthesis such coupled pairs into complex chains and cross braces, reconstructing the whole system in a quasi-mechanical way.

As Weiss explains, in practically all of our biological thinking the opinion still dominates that by application of this synthetic method science will eventually succeed in describing and comprehending all entities and processes in nature. Weiss states that physics has already begun to depart from such a micromechanistic attempt whereas biology has not. However, in an organism the mere reversal of the analytic dissection can yield no complete explanation of its behavior as a living system.

What is overlooked is that during isolation of A, B, etc. already a lot of information has been neglected in order to characterize these entities. However, especially in an organism, each entity depends upon the interactions with others. This means that in the absence of C neither A nor B can exist. The coexistence and co-operation of all three is indispensable for the existence and operation of any one of them. Only by artificially neglecting the so-called boundary conditions can A and B be studied in an isolated manner.

Experimentally, this procedure may often be adequate. Nonetheless, it is overseen that the information which is neglected during this process cannot be reconstructed through a synthesis from the knowledge of the properties of these parts. The analytical procedure has been very successful in science, but obviously it must

be complemented by a scientific method that regards the systems properties as well.

Weiss points out that only by virtue of their ordered interactions do molecules become partners in the living process. Since this involves vast numbers of compounds, all living phenomena consist of group behavior, which offers aspects not evident in the members of the group when observed singly. Weiss already mentions that this fact is generally obscured by referring to living systems as "complex", which has become quite fashionable these days.

3. System

Weiss points out that in contrast to the infinite number of possible interactions and combinations among the parts, in the living system only an extremely restricted selection from the opportunities for chemical processes is being realized at any one moment—a selection which can be understood solely in its bearing on the concerted harmonious performance of a task by the complex as a whole [32]. This is the feature that distinguishes a living system from a dead body or a functional process from a mere list of parts involved.

> "The systems concept is the embodiment of the experience that there are patterned processes which owe their typical configuration not to a prearranged, absolutely stereotyped, mosaic of single-tracked component performances, but on the contrary, to the fact that the component activities have many degrees of freedom, but submit to the ordering restraints exerted upon them by the integral activity of the 'whole' in its patterned systems dynamics." [32, p. 9]

This is the essential turning-point: Weiss sees a living system as an entity, which imposes restricting, i.e. regulating functions upon its component parts, so that the functionality of the whole system is ensured. The system itself contains constituting properties and thus possesses information, which does not stem from the parts themselves. The system must be regarded as a spatio-functional entity, which integrates the functions of its parts. He understands this as a "supra-molecular order in living systems".

Weiss expresses this in his working definition of a system: "Pragmatically defined, a system is a rather circumscribed complex of relatively bounded phenomena, which, within those bounds, retains a relatively stationary pattern of structure in space or of sequential configuration in time in spite of a high degree of variability in the details of distribution and interrelations among its constituent units of lower order." [32, p. 11].

Not only does the system maintain its configuration and integral operation in an essentially constant environment, but it responds to alterations of the environment by an adaptive redirection of its componential processes in such a manner as to counter the external changes in the direction of an optimal preservation of its systemic integrity.

One such system is the cell: the cell hosts a number of components such as organelles and molecules. However, the cellular system integrates all these components to a functional unit. It needs these components and depends heavily upon them, but the cell is only able to live due to the regulation, which is imposed on the components by the system.

"The basic characteristic of a system is its essential invariance beyond the much more variant flux and fluctuations of its elements or constituents."[32, p. 12]. Thus the elementary functions of a system may be quite variable. This corresponds exactly with modern knowledge of the cell: whether and when information is transcribed from the DNA, whether certain proteins are built or which components are included in the cell-membrane to keep it within an optimal stage of fluidity, is permanently changed according to the functional state of the cell and its environmental conditions.

> "This is exactly the opposite of a machine, in which the structure of the product depends crucially on strictly predefined operations of the parts. In the system, the structure of the whole determines the operation of the parts; in the machine, the operation of the parts determines the outcome."[32, p. 12]

4. Organisms as hierarchically ordered systems

A cell has sub-systems, namely, the organelles which perform partial processes. Thus a mitochondrion can be seen as a subsystem that integrates the molecular devices for processing energy. Looking at the next higher level beyond the cell, there is the tissue in which the cells are organized. Such a tissue is also a system in which functions of single cells are integrated and regulated. One example would be an epithelium, in which a boundary is established by systemic cooperation of many cells. In this case the system can have certain characteristics, such as a barrier, which are not characteristics of the single cells. They are a property of the association of the cells. A further possible level is constituted by the organs of an organism, like a heart, a lung or a liver. Finally the organism integrates all these sub-systems into a coherent whole.

Thus the integral systems operation, whether of the body as a whole or of an organ such as the brain within it, "deals with the molecules not directly, but only through the agency of intermediate subordinate sub-systems, regarded in a hierarchical scale of orders of magnitude. . .. Each sub-system dominates its own subordinate smaller parts within its own orbit or domain, as it were, restraining their degrees of freedom according to its own integral portion of the overall pattern, much as its own degrees of freedom have been restrained by the pattern of activities of the higher system of which it is a part and participant." [32, p. 14].

The tendency to imply a higher activity to molecules or genes vests them with animistic powers, Weiss states. This is still an inclination today: in many descriptions of the activity of proteins or steroid hormones and the like, the organism seems to be steered by such substances. The common term that is used is "control": a protein or gene "controls" a cellular process, a hormone "controls" the function of an organ. From an organismic perspective it would be more appropriate to state that the organism uses such signaling molecules to regulate its functions and to adapt them to current conditions. The most extreme form of such an obscure animism is genetic determinism, which is currently under pressure by recent developments in genetics and epigenetics.

Another feature is equally important: systems are not inherently closed. They have a relative stability and thus an organizational closure, but at the same time they are open for influences from their surroundings. Weiss demonstrates this using the example of the cell: a cell is a well characterized entity and can be regarded as a system. However, in a multi-cellular organism it needs to be regulated and thus must have a certain openness to regulative influences. To guarantee this the cells of multi-cellular animals have a multitude of membrane receptors, which mediate signals from the surrounding. They also need to have a regulated exchange of substances with the environment to maintain their basic functions as well.

Here, a first difficulty emerges: a system is relatively closed as well as relatively open at the same time. Coincidences of this type, where two opposing principles are present simultaneously, are a typical feature of organic life and can be found in many other examples as well. An organismic thinking has to take account of such properties. This is the reason why Weiss presents such a long-winded definition of a system as quoted above, using formulations like "relatively bounded", "relatively stationary" and so on.

Now we have the components together to understand Fig. 1, which represents the hierarchical order of the systems of an organism. Each system has a relative invariance and autonomy as well

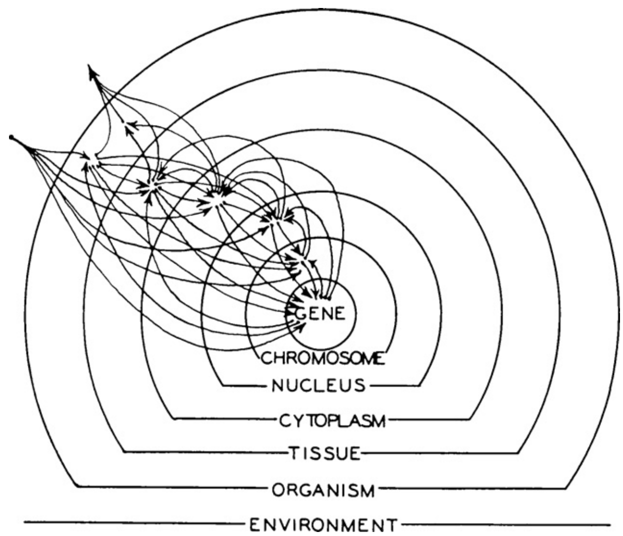

Fig. 1. Interactive relations among the hierarchically ordered subsystems of an organism [32].

as a relative openness to regulative influences from superimposed higher level systems. The arrows indicate pathways of possible interactions which must be taken into account in studying such an organism. Also, the whole organism cannot be regarded as a closed system. Rather it is integrated into its environment with many forms of exchange.

5. Ontogeny

Even the egg is such an open system. It is not only a nutrient solution for the genome, but rather a real organism, comparable to single-celled organisms. Today we know that the cytoplasm of the egg transports numerous components that are needed for normal development. Among these are basal bodies, the microtubule organization center, cytoplasmic gradients, different types of RNA, membranes and organelles like mitochondria, including their own DNA and many more.

Development then takes place through continuous interactions between factors of the cytoplasm and DNA, whereby DNA methylation patterns introduce additional levels of information. Within these processes the genetic information as well as the cytoplasmic factors are equally important, so that the idea that DNA determines development is one-sided. When the embryo develops into a multicellular organism, extracellular factors such as the position within the organism become additionally relevant. In each cell the relevant genetic information must be expressed at the right moment and at the appropriate place, which itself is dependent upon a spatial order as well as a temporal order, which in turn is important in itself and cannot simply be reduced to the genetic information.

To explain this principle Susan Oyama developed a theory which she calls "developmental systems theory" [37–41]. This theory is quite radical and it may be open for further discussion and insights from future empirical research, but it is interesting in regard to the question of interaction between different system levels. Oyama criticizes the notion that the genome is considered to be a force, which drives and determines development as well as the characteristics of an organism, a view that has been much discussed as "genetic determinism" (see for example [42–44]). For Oyama, however, a solution of the "nature versus nurture" debate is not that the environment also plays a certain role and modifies the genetically predetermined way. She argues that the information for the assembly of the organism can neither be found in the genome nor in the environment, but it is realized by the process of development within the developmental system.

Oyama assumes that DNA is only one of several factors for the process of development, albeit an important and necessary one. Nonetheless neither sequences of DNA nor any other factors can be privileged as bearers of ultimate causal control of the developing organism. Rather, the whole complex of factors is equally important to explain the appearance and the regularity of the steps: cellular morphology, the dynamic of biochemical processes, environmental influences, the previous history of the system and also the DNA sequences involved. DNA is just one of many resources within the entire process.

Thus chromosomes do not carry a recipe for the development. What is transmitted is only the information on how some necessary building blocks are to be synthesized. These building blocks may influence some characteristics of the organism, which we identify as inherited. The organic form is constructed during development as a result of interactive processes between the different levels of systems involved. This construction is continued throughout the entire life span and everything that appears, from the first cell divisions of the zygote to the moment of death of the organism, is actually generated. According to this view there is no genotypic plan, a program or a blueprint in the background, and development does not unfold according to a predetermined choreography. The choreography is always what actually happens, not a preformed regulation of steps.

Since the embryo is "constructed" during development, Oyama calls her approach "developmental constructivism". She also expands this principle beyond the time of the development of the embryo, so that each organism can be considered as continuously "self-constructing" during its whole lifetime. This becomes obvious in the permanent potential of regeneration not only of many tissues, but also of every cell, that continually recycles its organelles. In addition, many tissues are very plastic and are permanently adapted to actual requirements [45].

If one accepts the quite radical theory of Oyama it is not surprising that heredity can be found on different levels. The recent excitement about epigenetic principles of heredity in molecular biology results from the previously one-sided idea of genetic reductionism. According to the concepts of Oyama and Weiss this heredity is to be expected rather than being a surprise.

6. Changing autonomy in evolution

When looking at evolution it is obvious that these systems, as Weiss and Oyama describe them, have been generated stepwise. The earliest organisms were single-celled prokaryotes, still being the basis of our ecosystems today. They had a rich diversity of metabolic principles but a relatively simple cellular and morphological organization. Their functions of DNA expression were quite direct: while DNA is transcribed, the translation into proteins already begins. The transition from prokaryotes to eukaryotes brought about a cell type with a much more elaborate system of organelles and membranes, including more levels of regulation of gene expression. The generation of multicellular organisms by using eukaryotic cells as building blocks added the next systems level, which integrates the cells into a supracellular system. For this the eukaryotic cell became more adjustable within this higher level system, which was reached by many more signal functions such as receptors on the surface of the cell and the corresponding signal transductions within the cell [45].

When the principle of integrated multicellularity emerged, a large amount of different types of multicellular organisms evolved. This is known as the Cambrian explosion. Within a relatively

short time all different phyla of the animal world appeared. They included organisms with increasingly more elaborate organic systems, thus generating further system levels. It has been shown that this generation of system levels led to an increase in autonomy of the respective organisms [46–55]. Organisms gained in stability, self-regulation and self-assertion. The direct influences of the environment were gradually reduced and a stabilization of self-referential, intrinsic functions within the systems was generated. In higher animals this included the potential for more flexible and self-determined behaviors.

These processes were described as relative autonomy because numerous interconnections with the environment and dependencies upon it were retained. Features of an increasing autonomy are spatial separations from the environment, increases in homeostatic functions and in body size, internalizations and an increase in physiological and behavioral flexibility. Especially mammals and birds developed high degrees of autonomy compared to the other vertebrates and to invertebrates.

Autonomy reaches a special level in humans. First, there are those features we share with all mammals: a skin, which simultaneously closes relatively tight towards the environment and is highly flexible and light; endothermy combined with a high aerobic capacity enabling movements with endurance and to a large extent emancipated from variations in environmental temperatures; an effectively stabilized fluid management, including refined processes for homeostasis and highly efficient renal functions; a medium body size, which supports homeostatic functions, but does not generate a larger burden for movements; and an extremely refined immune system.

Then there are special features of humans, being the basis for a largely autonomous life that is cultivated today: our hands are completely freed from locomotory functions due to our upright posture and they have nearly unlimited possibilities of flexibility and dexterity. Humans are unique among primates in terms of relative brain size as well as some features of brain organization [56]. One special feature of the human brain is that its prefrontal cortex is disproportionately large. This enlargement helped to increase the ability of humans to suppress reflexive and instinctive responses to stimuli and as a result to increase their possibilities for self-control. The prefrontal cortex is also involved in planning complex behavior, expressing personality, decision making and moderating correct social behavior. The basic activity of this brain region is considered to be the orchestration of thoughts and actions in accordance with internal goals [56,57]. Thus the prefrontal cortex is essential for the most flexible, self-determined and thus autonomous actions of man.

With all this, a feature emerged in humans, which is clearly unparalleled within the animal world: the ability of self-control and willful, conscious behavior, with all the related qualities, which constitute a responsible person. The reduction of instinctive behavior is paralleled by large degrees of freedom in behavioral possibilities such as learning capacities, imitation, tool use, insight, empathy, self-reflection and speech. The history of mankind must be told in terms of autonomy, of increasing flexibility and degrees of freedom (for details see [46–48]).

Autonomy in this sense involves an intrinsic and an extrinsic component (constitutive and interactive autonomy according to Moreno [58,59]), which also corresponds to the description of systems by Weiss, as quoted above: a system efforts to stay constant although there is a much greater potential for variation of its components. Within certain limits this is still the case when parts and components are modified or exchanged (intrinsic autonomy). However, the system maintains its configuration and integral operation not only within a constant environment, but it also responds to alterations of the environment by an adaptive redirection of its processes in such a manner as to counter the external changes in the direction of an optimal preservation of its systemic integrity (external autonomy).

7. Synthesis

By synthesizing the elements from these three approaches it is possible to formulate a coherent, though preliminary concept of the organism: every living organism is characterized by a hierarchy of different level systems which are in simultaneous interdependencies with each other. The systems of each level generate circumscribed units, each with a spatial and temporal integrity. These units are equally constitutive for the system as their respective components. Ontogeny takes place by means of continuous interactions between the systems of different levels and the DNA information and in this way generates the supramolecular order. During evolution, the generation of system levels leads to an increase in the autonomy of organisms. This autonomy reaches a special combination in higher animals and humans.

8. Molecular systems biology

After being considered quite unconventional in biology before, recently much has been written about systems theory (see for example [60–62]). It was expected that the extensive knowledge about the molecular processes might be synthesized, so that the system may finally be reconstructed and the influence of the different parts could be studied. This process was thought to overcome the problems of reductionism. However, if one takes a closer look at the concepts involved, one realizes that they follow – admittedly with some differences – the synthetic method that Weiss criticized. This is shown by some definitions from the field. On the homepage of a large institute for systems biology the following definition of a system is offered: "One can broadly define a 'system' as a group of independent but interconnected elements that function together to comprise a unified whole. "Another definition is" Systems biology is the study of an organism, viewed as an integrated and interacting network of genes, proteins and biochemical reactions which give rise to life" (cited from [63]). These definitions express clearly the expectation that the parts in their manifold interaction generate the whole system. Accordingly, one just needs to regard the functions of all parts in order to get in the sum finally an understanding of the system. This, however, is not a viable way to overcome reductionism, but rather the attempt to carry it out continually. After the single factors have been studied, one tries to bring the components together, especially by using high performance computers.

Such an approach is unlikely to succeed. The respective functions of the system follow their own principles, which are obviously not generated from the combination of their parts. Up till today no one has ever demonstrated how the many components and processes finally build a cell. Also, for all previous manipulations in biotechnology, a complete living cell is essential, which provides the context factors necessary for the functioning of the manipulated parts. When Craig Venter claimed recently that he had made a fundamental step towards a synthetic cell, he used a living cell as a prerequisite and just introduced some synthetic molecules. This has nothing to do with producing new life from scratch [64].

Quite a body of literature exists already on this problem, but it is usually disregarded by most proponents of modern systems theory. Only few scientists are aware of the profound epistemological restrictions as clearly as Mesarovic and Sreenath [63], who see a "flat earth systems biology" in this new development and "that there are more stars to be reached" (p. 34). It is predictable that the promises of this trend will not be fulfilled, just as the promises of a too one-sided genetic approach were not redeemable either. This critique is essentially consistent with that of Drack and Wolken-

hauer [28] who state that the approach of today's systems biology is in major parts too narrow. Noble [4] does not walk into this trap in his beautiful little book while developing a systems approach that is quite near to the one of Weiss, however, again without referring to him.

Now the term "emergence" is also considered. It describes that properties emerge in a system, which are not predictable from the properties of the parts [65]. However, this hides the crucial problem. If "emergence" is understood in the sense of synthesis described above, it does not overcome the usual reductionistic point of view: the parts work together so that a new property emerges. Here, there would be no difference between a living organism and a machine: even a car is more than a heap of its components and a house is more than a heap of stones. In biology it has been expected that the integral network of molecular processes would build up the organism, as parts are put together to construct a functioning car.

The car is dependent upon the appropriate functioning of the combination of the separate parts. A living system, however, works the other way around: it, too, is dependent on having functioning components, but it is able to generate them itself, can regulate which components have to be increased or decreased, and it can vary them according to a time scale (e.g. a day or a season) or to a stage of development. Moreover, a living system can adapt all this to the respective environmental circumstances, so that the stability and autonomy of the system is maintained, even when it is confronted with changing environmental factors—as long as these changes are within certain limits. Moreover the loss of some components can often be compensated.

9. Current problems and open questions

Systems theory has been discussed in biology as well as in medicine for a long time. However, in some of its versions it tended to be too abstract and theoretical to develop a deeper impact on scientific reasoning. Only few disciplines were able to realize more concrete concepts, as for example ecology [1] or some topics of medical research [14,15].

The second problem is that the basic concept has not really been satisfactorily defined, while the impressively clear descriptions of Weiss are largely neglected. Today, the essential differences between the reductionist version of systems biology and an organismic systems biology are often overseen.

The concept that is developed here reaches far beyond the usual synthetic approach. It may need further elaboration, but it has some clear basic assumptions, which are concurrently developed with the phenomenology of the organism. However, such a new – or at least underdeveloped – concept yields problems and open questions. If we assume the systems model as it is shown in Fig. 1 the question arises how the respective levels of the hierarchical systems may be determined. The levels shown may only be one of several possibilities. Of course, they seem not to be arbitrary, since entities like a cell or an organ (e.g. the liver) have clear structural and functional boundaries. On other levels, like the tissue level, the respective connectivity can be more complicated.

A pragmatic question is: which empirical methods would be appropriate to study the respective features on the different levels? First, it can be said that the hierarchical concept provides a clarification of the competence of the different disciplines. Thus, molecular biology has the task to study the processes on the level of molecules. However, it is not appropriate to overextend its competence. Cell biology works on the level of the cell, histology on the level of tissues and so on.

Classical physiology mostly delivered insights in systems-level properties [4]. Possibly this work is able to generate still more essential insights. Thus, it may be a severe mistake to convert many institutes of physiology into molecular ones, especially as modern experimental technology may widen the possibilities to work on integrative systems levels.

Often it may be difficult to work on higher systems-levels and to achieve clear and reproducible results on them. Perhaps there will be something like an uncertainty principle: the further down we look at the parts, the more exactly we may be able to describe causal relations, at the same time losing the context out of sight. The further up we work on integrative levels the more we shall perceive from the context, but it might be more difficult to define exact factors and to come to a precise reproducibility. Such methodological difficulties should not mislead us to exclude a feature from scientific consideration. Otherwise one would act like the man who only searches where he has enough light, although he probably lost his keys in a different place.

Systems may include higher level laws which are not present in the part components. These laws seem to organize the coherent function of the whole complex. Noble [4] gives a persuasive example for this: we cannot locate the site of the pacemaker rhythm in the heart at the sub-cellular and molecular levels. Yet we have no difficulty in locating it at the level of certain cells within the whole organ. We know what it means to refer to the pacemaker of the heart and we can locate it anatomically. If a particular biological function or entity does not exist at one level, this does not mean to say it does not exist at all. The principle on a higher level obviously includes laws – "information" if you like – which are not reducible to the molecular level and thus stand on their own. We just have to go up or down the different levels to find the context in which certain organizing principles and laws can be found. In this sense, I agree with Noble that one of the important goals of integrative systems biology is to identify the levels at which the various functions exist and operate.

Another question is the nature of scientific accessibility of integrative functions of systems. This has largely been discussed under the term "downward causation" [15,66,67].

A further methodological question might concern the interrelation between part processes and system levels. In some of his descriptions, Weiss tends towards a predominance of the system levels over the part processes and thus seems to constitute some overweight towards holism (see also [28]). However, most likely, the task will be to see the simultaneous interrelation between the different levels—a view that is inherent in the concept of Weiss and perhaps quite subsequently realized in Oyama's theory. This interrelation, exhibited at any time by the organism, might pose one of the difficulties in the analysis of organismic functions in general. This is not to be found in the inorganic world. This principle is obviously responsible for the restrictions of unidirectional cause and effect explanations in life sciences, as soon as organic functions above the molecular level are considered. An organismic concept will have to regard this principle explicitly in order to avoid new traps of one-sidedness. Basically these principles have been much discussed in approaches like circular causality, complexity and nonlinear network dynamics and may still need a future synthesis with a hierarchical systems approach as it is outlined here. This is another coincidence of opposing principles like the simultaneous closure and openness of systems as discussed above.

10. Empirical evidence

Many results of modern research point into the direction which is developed here. For now just a few examples must suffice. Today it is well understood that the expression of DNA underlies a complex process of regulation. Signals from the cell are able to restrict or to activate the transcription of certain DNA segments. Under this

perspective the activity seems to come more from the cell system than from DNA. Salthe asserted, that the cell interprets its genome, thus turning around the usual interpretation [68].

A further example is that RNA is often extensively processed by splicing. Due to alternative splicing many different proteins can be generated from the same transcript. This means that the regulation as to which protein is really produced occurs within the cytoplasm. In other words: it is the system which regulates the process. The number of alternative mRNA-isoforms can be amazingly large.

The synthesis of a protein from mRNA can be stopped within the cytoplasm. Whether a protein is really produced in a certain place and at a certain time depends on the status of the cell, which can be modulated by many elements in the matrix of development. Thus it is incorrect to say that the information of the DNA contains functional information. Only a DNA-sequence together with a number of cytoplasmic factors, the protein folding and the respective cellular context contain an adequate amount of information to build a phenotypic property.

Even the decision which areas of DNA are transcribed underlies a cellular regulation. This has been extensively discussed recently in the field of epigenetics. According to Jablonka and Lamb [69] epigenetic inheritance in the broad sense is the inheritance of developmental variations, which do not stem from differences in DNA sequences or from persistent inducing signals in the present environment. In a narrower sense, inheritance is restricted by some authors to the transmission of chromatin marks and RNAs. The transmission of such marks obviously plays an important role in inheritance. Thus it becomes increasingly clear that beyond the level of DNA there are other levels in the cell, which bear information. This confirms exactly the prediction Weiss already formulated in the 1960s. The whole field of epigenetics is the most important one to study processes on the next higher level. The links between genotype and phenotype are much more complex than previously thought, and beyond that they can be much more dynamic.

One challenge for reductionism derives from the fact that the effect of a molecular entity or mechanism may strongly depend on the context in which it occurs [6,70]. It is well known today that a molecular pathway may have different effects in different cellular contexts, so that the same pathway can be involved in different functions in different species or in different parts of an individual. Even the amino acid sequence produced by a gene may depend on elements outside of this gene and non-genetic factors, so that a gene can code for distinct products in different cells or different states of a cell. Thus there is a one-to-many relation between molecular and higher level entities: a molecular mechanism can causally lead to or be part of different higher level states depending on the context [16].

Another example comes from evolutionary research. Since the sequences of whole genomes of organisms on different evolutionary levels are available, it has been convincingly demonstrated that corresponding sequences are too similar to each other to explain the diversity of the respective organisms and their different functions exclusively on the genetic level [71]. Related to this is also the enigma of why the genome of human beings is only less than 1% different from that of chimpanzees. Jablonka and Lamb [69] draw the consequences from this description of increasingly more levels of information and postulate that inheritance has four dimensions: the first two dimensions are the genetic and the epigenetic systems. Further levels are social learning, in which information can also be transmitted. This is present in many animals. The fourth dimension, which is present only in man, is speech and other forms of symbolic communication. As a result, Jablonka and Lamb view the basic assumption of neo-Darwinian theory as indefensible, according to which only changes on the level of DNA should be able to produce evolutionary variations. This even includes the inheritance of some non-random variations and acquired characters. These insights mark a new epoch in evolutionary science: "Our basic claim is that biological thinking about heredity and evolution is undergoing a revolutionary change. What is emerging is a new synthesis, which challenges the gene-centered version of neo-Darwinism that has dominated biological thought for the last fifty years." [69, p. 1]. This will also have consequences for our basic understanding of the organism.

Gerhart and Kirschner [45] discuss a problem which emerged with the new techniques of comparing sequences of proteins and DNA. Results from such comparisons showed that during evolution many genes and proteins underwent only minor changes. It had been expected that most changes would be found on the level of genes, but many genes and proteins are "highly conserved", staying largely unchanged, even when the organisms to which they belong – i.e. the system – underwent larger evolutionary changes. In addition, organisms are obviously able to integrate conserved genetic building blocks into a new context. On the other hand, single mutations often have amazingly little consequences for the protein product. One such example is the globin family, in which in some cases only 10–20% of the amino acids are identical without a change of the tertiary configuration of the proteins [45]. It can be assumed that the process of folding in the cytoplasm introduces an additional level of information.

The phenomenon of conserved genes tells us that evolutionary changes may also be generated by changes on higher system levels and not exclusively by genetic changes. There can be no doubt that genetic changes are important, but there seem to be additional levels, from which changes can be triggered [69,72]. Thus, there are many clues indicating that changes on higher system levels are important. "Evolution shapes systems, not genes" [73]. Other authors, too, try to focus more on the phenotype than focusing exclusively on the genotype [74,75] (for most recent developments in evolutionary biology see [76]).

In summary, we can say that many results of empirical research and of some recent considerations about them point into the direction the described concept of organismic systems biology proposes. Especially Weiss' concept delivers a sound foundation for the concept and is at the same time open enough to include new insights and developments from empirical research as well as theoretical reasoning.

Weiss was predominantly a – highly successful – experimental scientist for whom the system approach "remained simply a silent intellectual guide and helper in the conceptual ordering of experience..." [35, p. 18–19]. Thus Drack et al. [27] state: "The experimental biologist Weiss never developed a 'system theory'. Rather, from the insight he obtained by his experiments and observations, he described what such a theory must comprise and where the problems lie with the 'analytico-summative' approach, as well as its abstraction and shortcomings." I assume that this is the fairly sound background for the development of an approach close to the real organismal functions, while mere theoreticians often risk to be too far removed from organismal reality.

11. Medical research

The view of the organism as a multilevel complex of systems with integrative functions not only has consequences for biology in general, but also for medicine. However, my focus here is only on the human organism itself, the living body, not on the further aspects of man regarding mind and emotional life.

Large parts of modern biomedical science build heavily on an image of the organism that is basically reductionistic in character [14]. In its extreme version all properties are seen as a sum of the molecules involved and searching for the roots of common diseases is increasingly reduced to this level. Genetic reduction-

ism plays a crucial role in this search as it is expected that the cause of many diseases may be found on the genetic level. The work on this level is indeed necessary and at times even successful when defects at the molecular and genetic levels are really involved. However, disorders on this level are not a prototype of disease. Human disease phenotypes are controlled not only by genes but also by self-organizing networks, which display system-wide dynamics. Diseases are complex context-dependent entities to which our genes make a necessary, but only partial contribution [24]. The highly autonomous organism of humans has many regulative functions which are often able to restore an endangered autonomy. Thus, for example, our immune system is the most elaborate one compared to all animals [46]. Therefore, medicine urgently needs a more balanced approach to work on the different levels of organismic functions which are clearly definable according to the organismic systems concept. Widening modern biomedical work to these different organismic levels on the one hand, and including the mental aspects on the other comes nearer to a comprehensive image of man and disease.

From all that is known today, together with the concept of organismic systems theory proposed in the present paper it should be clear that the attempt to develop personalized medicine solely on the genetic level is a profound conceptual mistake; and it is predictable that it will fail simply because it fails reality [17,18,24]. The term personalized must include the different systemic levels of an organism and take into account the autonomous person in its multidimensional unity [77–79].

However, there are some fairly sound developments underway. For example, recent research suggests that some diseases may be associated with a deregulation of gene-expression, including epigenetic processes. These topics around epigenetics are now hotly debated in post-genomic times. In view of the systems approach developed here, one can state that due to the shift from genes to epigenetic gene regulation, the next higher level of organismal organization is being reached in molecular research. There has been some amazement in recent genetics about this picture. However, organismic systems biology would predict these developments.

The physician has to deal with these different levels of integrative functions, and we still do not know much about their respective relations, or briefly, between genotype and phenotype. Although epigenetics is beginning to build a bridge, this interrelationship is still a black box in many respects. Also, in many fields, the medical establishment still thinks too much in terms of causality when, instead, it should be searching for a much more appropriate thinking in the future regarding the interdependence of processes.

If, according to Oyama, systems are more the result of what actually happens between their components, including the permanent interactions between the different levels and their respective contribution, it may be a mistake for medicine to search too much for a pre-disposition of certain defects. There may be a spectrum, which reaches from some diseases having a stronger pre-disposition, genetically or environmentally, to others that underlie much more the actual history of a person, including the biography. However, this is what real life and daily practice in medicine suggest. Therefore, research (especially basic research) must be more balanced according to this spectrum. From this perspective it is not strange any more that monocygotic twins may develop very different histories of health and disease even when there is some genetic disposition involved which is rather to be expected. The same holds true for the mystery of why present cancer genes in some cases lead to the clinically manifest disease and others do not [12,80]. To know a lot about the genetics of disease is important, but it is worthless as long as the question is neglected: how does the system deal with its genome? This leads to a shift from focusing too strongly on the genetic preformation to the question of how the system is able to deal with its genetic prerequisites.

If the concept developed here is appropriate at least in its basic assumptions, it would be necessary to develop scientific techniques to observe different systems levels to find out, whether there are more disturbances on lower levels (genetic, molecular), on the next level of regulation (epigenetic) or on further, more integrative levels, including how to influence the functions of a person on these different levels. Thus it should be clear that the view from organismic systems theory integrates all that has been studied so far in recent research and does not oppose its results.

It is already common practice to acknowledge that therapies work at different levels. Sometimes a therapy works more on a regulative level and at other times the substitution of a substance is necessary. Thus the phenomenology of practical medicine already reflects the reality of the organism. Why should it then not be possible to give the organism an adequate concept in basic science?

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